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Re-examining NCTN Clinical Trials for Sex Differences in Outcomes and Toxicities in Patients with Neuroendocrine Neoplasms

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BACKGROUND

Prior large epidemiologic and retrospective studies have shown sex-based differences in the epidemiology and treatment-related side effects of patients with neuroendocrine neoplasms (NEN). The purpose of this study was to examine sex differences in outcomes and toxicities in National Clinical Trial Network (NCTN) NEN clinical trials.

METHODS

We performed a retrospective analysis of three randomized trials for patients with NEN conducted through the NCTN: ECOG-ACRIN E2211 [Phase II capecitabine + temozolomide versus temozolomide in advanced pancreatic NEN], SWOG S0518 [Phase III Octreotide + IFN versus Octreotide + Bevacizumab in advanced gastrointestinal NEN], and Alliance CALGB 80701 [Phase II everolimus versus everolimus + bevacizumab in advanced pancreatic NEN]. We examined sex differences in progression free survival (PFS), overall survival (OS), response rate (RR), and treatment-related toxicities as measured through NCI Clinical Trial Adverse Event Criteria.

RESULTS

The total number of males (M) and females (F) in each trial were E2211 (N = 73 M and 60 F), S0518 (N = 192 M and 210 F), and CALGB 80701 (N = 84 M and 66 F). The number of M and F within each treatment arm were E2211 [Capecitabine + Temozolomide (N = 38 M and 30 F) vs Temozolomide (N = 35 M and 30 F)], S0518 [Octreotide + IFN (N = 90 M and 112 F) vs Octreotide + Bevacizumab (N = 102 M and 98 F)] and CALGB 80701 [Everolimus (N = 40 M and 35 F) vs Everolimus + Bevacizumab (N = 44 M and N = 31 F)]. There were no statistically significant sex differences in PFS, OS and RR within the treatment arms of E2211, S0518 and CALGB 80701 clinical trials. However, there were sex differences in treatment-related toxicities in CALGB 80701 but not in E2211 and S0518.

In CALGB 80701, there was a higher occurrence of cardiac-related toxicities among females in Everolimus treatment (20% vs 3%; $p=0.022$) but not in Everolimus + Bevacizumab. In E2211, hematological toxicities showed a trend of female predominance in both treatment arms but not statistically significant.

CONCLUSIONS

Sex differences were present in cardiac treatment-related toxicities in CALGB 80701. However, there were no other statistically significant sex-based differences in PFS, OS, RR in the three clinical trials examined. Our findings suggest that sex differences in treatment-related toxicities in NEN may be more prevalent than previously recognized and highlight the need for further study in this area.

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